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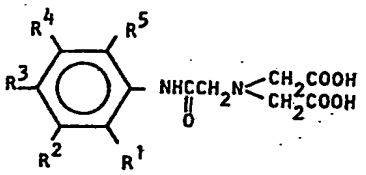
(54) NMR contrast agents.

(57) There are provided NMR contrast agents comprising water-soluble paramagnetic metal chelates, preferably of Cr(III), Fe(III) or Gd (III), wherein the chelating entity is an anilide group containing organic moiety, preferably a compound of formula I



(I)

wherein R^1 to R^5 may represent hydrogen or halogen atoms, optionally halogenated alkyl or alkyoxy groups or carboxyl groups. The agents are especially suitable for use in NMR imaging of the hepatobiliary system.

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GH 148-631

NMR Contrast Agents

The present invention relates to certain paramagnetic anilide-based chelates and their use as contrast agents in NMR imaging.

It has long been known that paramagnetic materials can be used to reduce the spin relaxation times in NMR spectroscopy. Recently, with the development of NMR imaging, an imaging technique particularly suitable for diagnostic application, the use of paramagnetic materials as NMR contrast agents has been proposed. Thus since the contrast in the NMR image is dependent strongly on the variation in relaxation times across the sample being imaged, the introduction of a material, such as a paramagnetic compound into a localised portion of the sample being imaged, e.g. into a particular body organ, will increase the contrast between that portion and the sample as a whole in the NMR image generated.

Paramagnetic compounds have been used in experimental NMR imaging for some years. Both soluble and insoluble paramagnetic compounds have been described in the literature although here we will only review the use of water-soluble compounds.

Compounds that exhibit paramagnetic properties are compounds which have unpaired electrons. The Table below shows some examples of paramagnetic compounds.

Table

Paramagnetic substances	
Paramagnetic metal ions	
Transition metals	Co^{2+}, Mn^{2+}, Cu^{2+}, Cr^{3+}, Fe^{2+}, Fe^{3+}
Lanthanides	Eu^{3+}, Gd^{3+}, Dy^{3+}, Ho^{3+}
Paramagnetic chelates*	MnEDTA, GdEDTA, MnDTPA, CoEDTA, CrDTPA, FeNTA
Stable free radicals	nitroxides
Molecules with unpaired electrons	O_2, NO, NO_2

*NTA = Nitrilo triacetic acid
EDTA = Ethylene diamine tetraacetic acid
DTPA = Diethylene triamine pentaacetic acid

Molecular oxygen has been used as a vascular paramagnetic contrast agent, but molecules such as NO and NO_2 are too toxic to be used in NMR imaging. Nitroxides however have been proposed as renal NMR contrast agents by Brasch et al in Radiology 147 (1983) 773.

Paramagnetic metals and chelates are now the most frequently used contrast agents in experimental NMR imaging. Manganese chloride ($MnCl_2$) has been used as an NMR contrast agent in animal studies, but the salt is probably too toxic for use in in vivo human experiments. Other paramagnetic ions such as Gd^{3+}, Dy^{3+}, Ho^{3+}, Fe^{3+} and Cr^{3+} have also been used in in vitro or in in vivo NMR experiments.

Schering AG in EP-A-71564 describe the preparation and use in NMR imaging of salts of paramagnetic chelates such as MnEDTA, DyEDTA, HoEDTA, and GdDTPA. Stable EDTA and DTPA chelates are excreted in the

urine and thus are potential parenteral NMR contrast agents for the enhancement of renal structures.

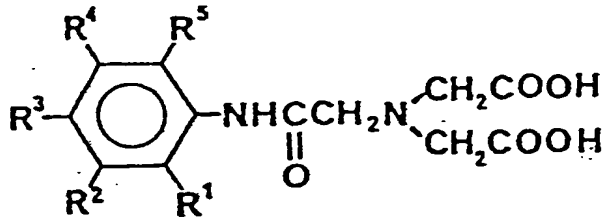
Paramagnetic chelates with desferrioxamine B, glucoheptonic acid and inositol hexaphosphoric acid have also been used as renal contrast agents in NMR imaging. A selective decrease in relaxation times of infarcted myocardium with the use of manganese-labelled monoclonal antibody has been shown.

Various particulate paramagnetic compounds have been studied for reticuloendothelial enhancement in NMR imaging of the liver, the particulate material being trapped in the reticuloendothelial system. We are unaware however that as yet any soluble paramagnetic chelates have been described as a parenterally administrable NMR contrast agent concentrating in the the liver or the bile.

We have now found that certain soluble anilide-based paramagnetic chelates can be administered orally or parenterally, e.g. by intravenous injection, to achieve a contrast effect in NMR imaging, e.g. of the liver and the bile.

In one aspect, the invention thus provides an NMR contrast agent comprising at least one water-soluble paramagnetic metal chelate together with at least one physiologically acceptable carrier or excipient, wherein the chelating entity is an anilide group containing organic moiety, more particularly, an anilide derivative of an imino polyacetic acid (i.e. a compound having at least three N-attached acetic acid residues one of which is converted into an anilide derivative while at least two remain as free acid groups).

The chelates in the contrast agent of the invention preferably have high lipophilicity and particularly preferably are complexes of a paramagnetic metal, e.g. a paramagnetic lanthanide or transition metal, with a chelating agent of formula I



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(wherein R^1 to R^5, which may be the same or different, each represent hydrogen or halogen atoms, optionally halogenated alkyl or alkoxy groups or carboxyl groups) or physiologically acceptable salts thereof.

In the chelating entity, R^1 to R^5 are conveniently optionally halogenated lower (C_{1-4}) alkyl or alkoxy groups but preferably are hydrogen, fluorine, lower (i.e. C_1-C_4) alkyl, or fluorinated lower alkyl (e.g. CF_3). Particularly preferably R^1 to R^5 are fluorine, or R^1, R^3 and R^5 are hydrogen and R^2 and R^4 are $-CF_3$, or R^1 and R^5 are lower alkyl and R^2 to R^4 are hydrogen.

We have found that the contrast agents of the invention are particularly effective as hepatobiliary contrast agents when the paramagnetic metal in the chelate is a trivalent cation, especially preferably Cr^{3+}, Fe^{3+} or Gd^{3+}.

The chelates of the non-radioactive paramagnetic metals with compounds of formula I or salts thereof are novel and thus in a further aspect the invention provides a water-soluble paramagnetic chelate, for example of chromium or gadolinium, wherein the chelating entity is the residue of a compound of formula I or a physiologically acceptable salt thereof.

The chromium (III) chelate of N-(2,6-diethylphenyl-carbamoylmethyl) iminodiacetic acid and its salts are particularly preferred.

Certain chelating agents of formula I are known and their chelates with ^{99m}Tc have been used as cholescintigraphic agents. These "technetium chelates" are described for example by Nunn et al in J. Nucl. Med 24 (1983) 423 and Loberg et al in J. Nucl. Med. 17 (1976) 633 and are found to possess low renal secretion, high hepatobiliary specificity and rapid hepatocellular transit times.

Certain of the chelating agents of formula I however are novel and thus in another aspect the invention provides N-[3,5-bis(trifluoromethyl)phenylcarbamoylmethyl]iminodiacetic acid and the physiologically acceptable salts thereof. This novel compound may be prepared by reacting disodium iminodiacetic acid with ω-chloro-3,5-bis(trifluoromethyl)acetanilide, and its salts may be prepared in conventional ways from the free acid and a physiologically acceptable base.

In a still further aspect, the invention provides a process for the preparation of an NMR contrast agent according to the invention, which process comprises admixing in aqueous solution an anilide group containing chelating agent (e.g. a compound of formula I or physiologically acceptable salt thereof) and an at least sparingly soluble paramagnetic metal compound, e.g. a water-soluble paramagnetic metal salt the counterion whereof is physiologically acceptable or an at least sparingly soluble oxide or carbonate, optionally in suspension.

In a yet further aspect the invention provides a process for the preparation of a water-soluble non-radioactive paramagnetic chelate according to the invention, which process comprises admixing in aqueous solution a chelating agent of formula I or a physiologically acceptable salt thereof and an at least sparingly soluble paramagnetic metal compound, e.g. a water-soluble paramagnetic metal salt the counterion whereof is physiologically acceptable

or an at least sparingly soluble oxide or carbonate, optionally in suspension.

Where chelate formation is by reaction of a compound of formula I with a trivalent paramagnetic ion, this is preferably achieved by reaction of one equivalent of the paramagnetic metal with two equivalents of the chelating entity.

The contrast agents of the invention may be pre-formed or may alternatively be prepared directly before administration by mixing in aqueous solution the chelating agent and a soluble compound containing the paramagnetic metal e.g. in salt form with a physiologically acceptable counter ion, for example a halide, such as chloride. Where the chelating entity is itself in salt form the counter ion should also be physiologically acceptable and may for example be meglumine or an alkali metal ion such as sodium. With the chelating agents of formula I, chelate formation appears to happen within a few seconds at from ambient temperature to the boiling temperature of the solution.

Thus in another aspect the invention provides a kit comprising a water-soluble paramagnetic metal compound, e.g. a Gd^{3+}, Cr^{3+} or Fe^{3+} compound, and an anilide-based chelating agent; either or both being optionally in solution in a physiologically acceptable carrier solvent, e.g. water for injections.

Where the contrast agent of the invention is supplied in the form of a solution of the paramagnetic chelate in a physiologically acceptable carrier solvent, e.g. water for injections, the solution may be in concentrated form for dilution before administration.

As it is preferred that the contrast agent of the invention be at physiological pH, it may also contain a buffer.

Administration of the contrast agents of the invention is preferably by intravenous injection

of solutions containing the paramagnetic chelate in sufficient concentration to provide the desired hepatobiliary NMR-contrast effect. In this respect solutions containing the paramagnetic metal in concentrations of from 0.1 to 200 mM are suitable. Alternatively the contrast agents are formulated in forms suitable for oral administration, e.g. solutions, tablets or capsules.

The contrast agents may conveniently be administered in amounts of from 10^{-4} to 10^{-1} mmol paramagnetic metal/kg bodyweight.

Thus in a still further aspect, the invention provides a method of generating an NMR image suitable for use in diagnosis which method comprises administering an NMR contrast agent of the invention to a human or animal subject and generating an NMR image of at least a part of said subject in which said contrast agent is present.

A preferred embodiment of the method of the invention comprises NMR imaging wherein hepatobiliary contrast enhancement is achieved by administering an effective amount of at least one chelate of a paramagnetic metal (preferably Cr^{3+}, Fe^{3+} or Gd^{3+}) with an anilide-based chelating agent (preferably the residue of a compound of formula I or a salt thereof) intravenously to a human or animal subject and generating an NMR image of the liver and/or biliary system of said subject.

In a yet further aspect, the invention thus provides the use of a water-soluble paramagnetic metal chelate wherein the chelating entity is an anilide group containing organic moiety for the manufacture of a diagnostic agent for use in diagnosis of the human or animal body using NMR imaging.

Our experiments have shown chelates according to the invention to be efficient relaxation agents in vitro and to have high hepatobiliary specificity and rapid hepatocellular transit times. Thus in

a rabbit, after intravenous injection of 0.0075 mmol gadolinium/kg bodyweight in the form of a chelate with a compound of formula I in which the phenyl moiety is a 2,6-dimethyl-phenyl group, the contrast enhancement of the liver and the intestine 15 minutes after injection was very good. At this time the contrast agent had started to excrete from the liver. The chelate did not, however, show any contrast enhancement of the kidneys.

The rabbit was killed 1 hour after the injection, and the relaxation times in the liver and the kidneys were measured. The relaxation times in these organs were normal, which shows that all of the chelates had left the liver during the first hour. The quality of the NMR picture obtained with this chelate was much better than the general standard of NMR pictures published in the literature.

The contrast agents and chelates of the invention will now be illustrated further by the following non-limiting Examples:

Intermediate 1

N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid

The title compound was prepared from ω-chloro-2,6-dimethylacetanilide and iminodiacetic acid by the procedure described by Callery et al. in J. Med. Chem. 19 (1976) 962. The product was isolated in 75% yield following reflux of the mixture for 3 hours; m.p. 216-217°C

Intermediate 2

N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid

The title compound was prepared from ω-chloro-2,6-diethylacetanilide and iminodiacetic acid in a manner analogous to the preparation of Intermediate 1. The mixture was refluxed for 5 hours; yield 75%

m.p. 187-188°C

Intermediate 3

N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid

The title compound was prepared from ω-chloro-2,4,6-trimethylacetanilide and iminodiacetic acid in a manner analogous to the preparation of Intermediate 1. The mixture was refluxed for 4½ hours; yield 79%;

m.p. 220-221°C.

Intermediate 4

N-(2,3,4,5,6-pentafluorophenylcarbamoylmethyl)iminodiacetic acid

The title compound was prepared from ω-chloro-2,3,4,5,6-pentafluoroacetanilide and iminodiacetic acid in a manner analogous to the preparation of Intermediate 1. The mixture was refluxed for 1 hour; yield: 78%;

m.p. 182-183°C

EXAMPLE 1

N-[3,5-Bis(trifluoromethyl)phenylcarbamoylmethyl] iminodiacetic acid

Chloroacetyl chloride (17.8 g = 157.5 mmol) was added dropwise to a solution of 3,5-bis(trifluoromethyl)-aniline (34.4 g = 150 mmol) and triethylamine (15.2 g = 150 mmol) in toluene (300 ml) under cooling on ice. The temperature was slowly adjusted to ambient temperature and the reaction mixture was stirred for 1½ hours. Toluene was removed by distillation and the oily residue was washed with H_2O (300 ml). The oily residue was suspended in H_2O (300 ml) and placed in the refrigerator overnight. The precipitate was isolated by filtration and dissolved in boiling n-hexane (400 ml). The solution was filtered and cooled to ambient temperature. The crystals of ω-chloro-3,5-bis(trifluoromethyl)acetanilide were isolated by filtration. Yield 80%; m.p. 87-88°C.

Disodium iminodiacetic acid (37.2 g = 210 mmol) and ω-chloro-3,5-bis(trifluoromethyl)acetanilide (30.6 g = 100 mmol) were dissolved in a solution of ethanol-water (50:50) at 80°C. After 5 hours the ethanol was removed by distillation and the residue was extracted with diethylether (3 x 60 ml). The ether was removed by distillation and the pH was adjusted to 2. The precipitate was filtered off and washed with dilute HCl (200 ml), dissolved in boiling ethanol (400 ml) and precipitated with H_2O (750 ml). The title compound was isolated by filtration. Yield 22.2 g (55%); m.p. 201°C.
^{1}H-NMR(DMSO-d_6): δ 3.77 (s;-CH_2-), 7.72 and 8.37 (Ph), 11.20 (s; COOH), 11.54 (broad s, -NH-).
^{13}C-NMR(DMSO-d_6): δ 56.0 (-CH_2-), 59.1 (-CH_2-), 105.3-

141.6 (Ph and $-CF_3$)
Calculated (for
$C_{14}H_{12}F_6N_2O_5$) : C 41.80, H 3.01, N 6.96, F 28.34
Found : C 41.87, H 3.23, N 7.30, F 28.20

General procedure for formation of a gadolinium (III)-, iron (III)- and chromium (III) chelate with Intermediates 1 to 4 and Example 1

An aqueous solution of the disodium salt of the chelating agent (1 equivalent) and the metal (III) chloride hexahydrate (2 equivalents) was stirred and refluxed for one hour. The stirring was continued for one hour at ambient temperature. The pH was adjusted to 1.5 with dilute HCl and the metal chelate was isolated by filtration.

General procedure for formation of a manganese (II)-, copper (II), cobalt (II)-, and nickel (II) chelate with Intermediates 1 to 4 and Example 1

An aqueous solution of the disodium salt of the chelating agent (1 equivalent) and the hydrated metal (II) choride (1 equivalent) was stirred and heated to boiling. After cooling to ambient temperature the stirring was continued for one hour. The metal chelate was isolated by filtration.

EXAMPLE 2

Gadolinium (III) chelate of N-(2,6-dimethylphenyl-carbamoylmethyl)iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 72.2%, M.p. > 350°C. Solubility as sodium salt in water: > 0.02 M.
Analysis : $C_{28}H_{32}N_4O_{10}GdNa$.

Calculated : C 43.96, H 4.21, N 7.32, Gd 20.56, Na 2.73
Found : C 43.76, H 4.38, N 7.16, Gd 20.30, Na 2.70

Specific relaxation rate enhancement (SRRE) was measured in a NMR proton spin analyzer (RADX Corp., Houston, Texas, USA) at 10 MHz in glycerol: water 1:2 (v:v) at 37°C: 5.22 s^{-1} mM^{-1}.

EXAMPLE 3

Gadolinium (III) chelate of N-(2,6-diethylphenyl-carbamoylmethyl) iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 63%. M.p.: > 350°C. Solubility as sodium salt in water: > 0.1 M.

EXAMPLE 4

Gadolinium (III) chelate of N-(2,4,6-trimethylphenyl-carbamoylmethyl) iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 66%. M.p.: > 350°C. Solubility as sodium salt in water: > 0.1 M.

EXAMPLE 5

Gadolinium (III) chelate of N-(2,3,4,5,6-pentafluoro-phenylcarbamoylmethyl) iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 43%. M.p.: > 350°C. Solubility as sodium salt in water: > 0.1 M.

EXAMPLE 6

Gadolinium (III) chelate of N-[3,5-bis(trifluoromethyl)-phenylcarbamoylmethyl] iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 79%. M.p.: > 350°C. Solubility as sodium salt in water: > 0.1 M.

EXAMPLE 7

Iron(III) chelate of N-(2,6-dimethylphenyl-carbamoylmethyl) iminodiacetic acid

The iron(III) chelate was isolated as light yellow powder. Yield: 85%. M.p.: 220°C (decomp).
Analysis : $C_{28}H_{33}N_4O_{10}Fe$
Calculated : C 52.43, H 5.19, N 8.74, Fe 8.71
Found : C 51.59, H 5.23, N 8.63, Fe 8.71
SRRE : 1.86 s^{-1} mM^{-1}

Preparation of the meglumine salt of the iron(III) chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

The iron(III) chelate of N-(2,6-dimethylphenylcarbamoyl-methyl) iminodiacetic acid (160 mg = 0.25 mmol) was dissolved in methanol (20 ml) and N-methylglucamine (49 mg = 0.25 mmol) was added over a period of 15 minutes. The solution was evaporated to dryness and the meglumine salt of the iron(III) chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid was isolated as yellow crystals in a quantitative yield.

EXAMPLE 8

Iron(III) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid

The iron(III) chelate was isolated from a 0.14 M solution as a light yellow powder. Yield: 63%, M.p.: 250°C (decomp.)

EXAMPLE 9

Iron(III) chelate of N-(2,4,6-trimethylphenylcarbamoyl-methyl) iminodiacetic acid

The iron(III) chelate was isolated from a 0.04 M solution as light yellow powder. Yield: 88%. M.p.: 200°C. (decomp.)

EXAMPLE 10

Iron(III) chelate of N-[3,5-bis(trifluoromethyl)phenyl-carbamoyl-methyl)] iminodiacetic acid

The iron(III) chelate was isolated from a 0.04 M solution as light yellow powder. Yield: 78%. M.p.: 200°C (decomp.)

EXAMPLE 11

Chromium(III) chelate of N-(2,6-dimethylphenylcarbamoyl-methyl) iminodiacetic acid

The chromium(III) chelate was isolated from a 0.03 M solution as grey powder. Yield: 68%. M.p.: $>$ 320°C.

The meglumine salt of the complex was prepared in the same way as described in Example 12 (A).

Analysis : $C_{35}H_{50}N_5O_{15}Cr$

Calculated : C 50.48, H 6.05, N 8.41, Cr 6.24

Found : C 50.68, H 5.82, N 7.83, Cr 6.81

EXAMPLE 12

Chromium(III) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid and its meglumine salt

The chromium(III) chelate was isolated from 0.14 M solution as grey powder.

Yield: 71%. M.p.: > 320°C.

(A) Preparation of the meglumine salt of the chromium (III) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid

To a solution of the chromium(III) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid (140 mg = 0.2 mmol) in methanol (38 ml) was added N-methylglucamine (39 mg = 0.2 mmol) over a period of 15 minutes. The solution was evaporated to dryness and the meglumine salt of the complex was isolated as a pink powder in a quantitative yield. M.p.: > 320°C. Relaxation time (T_1) of a 10 mM solution of the product in water was 158 msec. T_1 (pure water): 3300 msec.

(B) Preparation of chromium(III) chelate of N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid and its meglumine salt

N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid (1.29 g = 4 mmol) and freshly prepared $Cr(OH)_3$ (206 mg = 2 mmol) was suspended in H_2O (250 ml). N-methylglucamine (390 mg = 2 mmol) was added in small portions while the suspension was stirred and heated at 95°C for 48 hours. The pink reaction mixture was filtered and evaporated to dryness. The meglumine salt of chromium(III) - N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid was isolated in 98% yield as pink powder.

EXAMPLE 13

Chromium(III) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid

The chromium(III) chelate was isolated from a 0.28 M solution as grey powder.
Yield: 63%. M.p.: > 320°C.

EXAMPLE 14

Cobalt(II) chelate of N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid

The cobalt(II) chelate was isolated from a 0.2 M solution as a pink powder. Yield: 59%, M.p.: > 300°C.
T_1 (10 mM; H_2O): 698 msec.

EXAMPLE 15

Cobalt(II) chelate of N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid

The cobalt(II) chelate was isolated from a 0.27 M solution as a pink powder.
Yield: 90%. M.p.: >300°C.
Analysis : $C_{16}H_{20}N_2O_5Co$
Calculated : C 50.67, H 5.31, N 7.39, Co 15.54
Found : C 50.70, H 5.54, N 7.00, Co 14.90

EXAMPLE 16

Cobalt(II) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid

The cobalt(II) chelate was isolated from a 0.11 M solution as pink powder. Yield: 86%. M.p.: >300°C

EXAMPLE 17

Cobalt(II) chelate of N-[3,5-bis(trifluoromethyl)phenylcarbamoylmethyl)] iminodiacetic acid

The cobalt(II) chelate was isolated from a 0.18 M solution as pink powder. Yield: 87%. M.p.: >300°C.

EXAMPLE 18

Copper(II) chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

The copper(II) chelate was isolated as a light blue powder. Yield: 76%. M.p.: 270°C(decomp.).
Analysis : $C_{14}H_{16}N_2O_5Cu$
Calculated : C 47.26, H 4.53, N 7.87, Cu 17.86
Found : C 47.35, H 4.63, N 7.47, Cu 17.04

EXAMPLE 19

Copper(II) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid

The copper(II) chelate was isolated from a 0.27 M solution as a light blue powder. Yield: 63%. M.p.: 250°C (decomp.)

EXAMPLE 20

Copper(II) chelate of N-(2,4,6-trimethylphenylcarbamoyl-methyl) iminodiacetic acid

The copper(II) chelate was isolated from a 0.11 M solution as a light blue powder. Yield: 62%. M.p.: 250°C (decomp.)

EXAMPLE 21

Manganese(II) chelate of N-(2,6-dimethylphenylcarbamoyl-methyl) iminodiacetic acid

The manganese(II) chelate was isolated from a 0.27 M solution as a white powder. Yield: 57%. M.p.: $>$ 350°C.

EXAMPLE 22

Manganese(II) chelate of N-(2,6-diethylphenylcarbamoyl-methyl)iminodiacetic acid

The manganese(II) chelate was isolated from a 0.32 M solution as a white powder. Yield: 80%. M.p.: > 350°C.

Analysis : $C_{16}H_{20}N_2O_5Mn$
Calculated : C 51.21, H 5.37, N 7.46, Mn 14.64
Found : C 51.80, H 5.69, N 7.27, Mn 14.90

EXAMPLE 23

Manganese(II) chelate of N-(2,4,6-trimethylphenylcarbamoyl-methyl) iminodiacetic acid

The manganese(II) chelate was isolated from a 0.36 M solution as a white powder.
Yield: 62%. M.p.: > 350°C.

EXAMPLE 24

Manganese(II) chelate of N-(2,3,4,5,6-pentafluorophenyl-carbamoylmethyl) iminodiacetic acid

The manganese(II) chelate was isolated from a 0.24 M solution as a white powder.
Yield: 47%. M.p.: > 350°C
Analysis : $C_{12}H_7F_5N_2O_5Mn$
Calculated : C 35.23, H 1.72, N 6.85, Mn 13.4
Found : C 35.18, H 1.97, N 6.53, Mn 12.9

EXAMPLE 25

Manganese(II) chelate of N-[3,5-bis(trifluoromethyl)phenylcarbamoylmethyl)] iminodiacetic acid

The manganese(II) chelate was isolated from a 0.18 M solution as white powder.
Yield: 82%. M.p.: >350°C

EXAMPLE 26

Nickel(II) chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

The nickel(II) chelate was isolated as a light green powder. Yield: 30%. M.p.: >300°C.
T_1 (10 mM; H_2O): 311 msec.

EXAMPLE 27

Nickel(II) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid

The nickel(II) chelate was isolated from a 0.27 M solution as a light green powder.
Yield: 42%. M.p.: > 300°C

EXAMPLE 28

Nickel(II) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl) iminodiacetic acid

The nickel(II) chelate was isolated from a 0.11 M solution as light green powder.
Yield: 38%. M.p.: >300°C.

EXAMPLE 29

Nickel(II) chelate of N-[3,5-bis(trifluoromethyl)phenylcarbamoylmethyl)] iminodiacetic acid

The nickel(II) chelate was isolated from a 0.09 M solution as light green powder.
Yield: 87%. M.p.: >300°C.

Preparation of solutions for NMR imaging from isolated chelates

EXAMPLE 30

Manganese chelate of N-(2,6-dimethylphenylcarbamoylmethyl)-iminodiacetic acid

An autoclaved isotonic 30 mM solution of the manganese chelate of N-(2,6-dimethylcarbamoylmethyl)-iminodiacetic acid in a 10 ml vial was prepared from:

Chelate of Example 21		104 mg
Sodium chloride		81 mg
Aqua purificata	ad	10 ml

EXAMPLE 31

Gadolinium chelate of N-(2,6-dimethylphenylcarbamoyl methyl)iminodiacetic acid

An autoclaved isotonic 13 mM solution of the sodium salt of the gadolinium chelate of N-(2,6-dimethylcarbamoylmethyl)iminodiacetic acid in a 10 ml vial was prepared from:

Sodium salt of the chelate of Example 2		100 mg
Sodium chloride		84 mg
Aqua purificata	ad	10 ml

EXAMPLE 32

Preparation of capsules for oral use

Chromium(III) chelate of N-(2,6-diethylphenyl-carbamoylmethyl) iminodiacetic acid (Example 12)	306.4 mg
Amylum maydis	q.s.

The powder was mixed and filled in capsules. (Capsule size 0). Each capsule contained 25 mg chromium.

Preparation of solutions for NMR imaging in situ:

EXAMPLE 33

Manganese chelate of N-(2,3,4,5,6-pentafluorophenyl-carbamoylmethyl)iminodiacetic acid

Solution A

An autoclaved isotonic 28 mM solution of the disodium salt of N-(2,3,4,5,6-pentafluorophenyl-carbamoylmethyl)iminodiacetic acid in a 20 ml vial was prepared from:

N-(2,3,4,5,6-pentafluorophenyl-

carbamoylmethyl)-iminodiacetic acid 100 mg
Sodium hydroxide 2 equivalents*
Sodium chloride 68 mg
Aqua purificata ad 10 ml

*(i.e. 2 equivalents of the N-(2,3,4,5,6-pentafluorophenylcarbamoylmethyl)iminodiacetic acid)

Solution B

An autoclaved isotonic 25 mM solution of manganese chloride in a 10 ml vial was prepared from:

Manganese chloride (36.8% H_2O) 50 mg
Sodium chloride 69 mg
Aqua purificata ad 10 ml

The chelate was prepared by adding solution B to solution A. After mixing, the solution is ready for use.

EXAMPLE 34

Gadolinium chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid

Solution A

An autoclaved 60 mM isotonic solution of the disodium salt of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid in a 20 ml vial was prepared from:

N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid 228 mg
Sodium hydroxide 2 equivalents
Sodium chloride 36 mg
Aqua purificata ad 10 ml

Solution B

An autoclaved isotonic 25 mM solution of gadolinium chloride in a 10 ml vial was prepared from:

Gadolinium chloride (35.9% H_2O) 66 mg
Sodium chloride 69 mg
Aqua purificata ad 10 ml

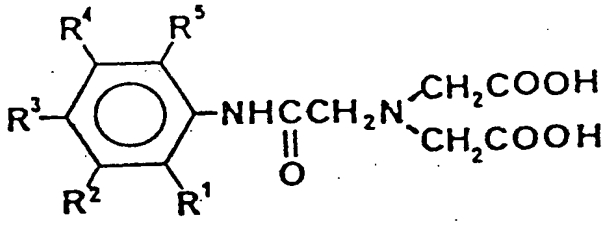
The chelate was prepared by adding solution B to solution A. After mixing, the solution is ready for use.

GG 148-631(1)

CLAIMS

1. An NMR contrast agent comprising at least one water-soluble paramagnetic metal chelate together with at least one physiologically acceptable carrier or excipient, wherein the chelating entity is an anilide group containing organic moiety.

2. A contrast agent as claimed in claim 1 wherein said chelate is a chelate with a chelating agent of formula I



(I)

(wherein R^1 to R^5, which may be the same or different, each represent hydrogen or halogen atoms, optionally halogenated alkyl or alkoxy groups or carboxyl groups) or a physiologically acceptable salt thereof.

3. A contrast agent as claimed in either of claims 1 and 2 wherein said chelate is a chelate of a trivalent metal ion.

4. A contrast agent as claimed in claim 3 wherein said chelate is a chelate of a metal ion selected from the group consisting of Cr^{3+}, Fe^{3+} and Gd^{3+}.

5. A contrast agent as claimed in any one of claims 1 to 4 comprising from 0.1 to 200 mM of said paramagnetic metal in aqueous solution.

6. A contrast agent as claimed in any one of claims 2 to 5 wherein said chelate is a chelate with a chelating entity of formula I (as defined

in claim 2 and wherein R^1 to R^5 are fluorine atoms or R^1, R^3 and R^5 are hydrogen atoms and R^2 and R^4 are trifluoromethyl groups, or R^1 and R^5 are C_{1-4} alkyl groups and R^2 to R^4 are hydrogen atoms) or a physiologically acceptable salt thereof.

7. A water-soluble non-radioactive paramagnetic chelate wherein the chelating entity is the residue of a compound of formula I as defined in claim 2 or a physiologically acceptable salt thereof.

8. A chelate as claimed in claim 7 of a trivalent metal ion.

9. A chelate as claimed in claim 8 wherein said metal ion is selected from the group consisting of Cr^{3+}, Fe^{3+} and Gd^{3+}.

10. A chelate as claimed in any one of claims 7 to 9 wherein in said chelating entity of formula I R^1 to R^5 are fluorine atoms or R^1, R^3 and R^5 are hydrogen atoms and R^2 and R^4 are trifluoromethyl groups, or R^1 and R^5 are C_{1-4} alkyl groups and R^2 to R^4 are hydrogen atoms.

11. N-[3,5-Bis(trifluoromethyl)phenylcarbamoylmethyl] iminodiacetic acid and physiologically acceptable salts thereof.

12. A method of generating an NMR image suitable for use in diagnosis which method comprises administering an NMR contrast agent as claimed in claim 1 to a human or animal subject and generating an NMR image of at least a part of said subject in which

said contrast agent is present.

13. The use of a chelate as defined in any one of claims 1 to 10 for the manufacture of a diagnostic agent for use in diagnosis of the human or animal body using NMR imaging.

14. A process for the preparation of an NMR contrast agent which process comprises admixing in aqueous solution an anilide group containing chelating agent and an at least sparingly soluble paramagnetic metal compound.

15. A process for the preparation of a water-soluble non-radioactive paramagnetic chelate which process comprises admixing in aqueous solution a chelating agent of formula I (as defined in claim 2) or a physiologically acceptable salt thereof with an at least sparingly soluble non-radioactive paramagnetic metal compound.

European Patent Office

EUROPEAN SEARCH REPORT

0165728
Application number

EP 85 30 3757

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	EP-A-0 012 967 (HOECHST) * Claims *	1-2	C 07 C 103/50 A 61 K 49/00
Y	GB-A-2 090 252 (SQUIBB) * Claims *	1-2	
D,Y	EP-A-0 071 564 (SCHERING) * Claims *	1-15	
P,Y	EP-A-0 130 934 (SCHERING) * Claims *	1-15	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 C 103/00
A 61 K 49/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	05-09-1985	MOREAU J.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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& : member of the same patent family, corresponding document

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

The present invention relates to certain paramagnetic anilide-based chelates and their use as contrast agents in NMR imaging.

It has long been known that paramagnetic materials can be used to reduce the spin relaxation times in NMR spectroscopy. Recently, with the development of NMR imaging, an imaging technique particularly suitable for diagnostic application, the use of paramagnetic materials as NMR contrast agents has been proposed. Thus since the contrast in the NMR image is dependent strongly on the variation in relaxation times across the sample being imaged, the introduction of a material, such as a paramagnetic compound into a localised portion of the sample being imaged, e.g. into a particular body organ, will increase the contrast between that portion and the sample as a whole in the NMR image generated.

Paramagnetic compounds have been used in experimental NMR imaging for some years. Both soluble and insoluble paramagnetic compounds have been described in the literature although here we will only review the use of water-soluble compounds.

Compounds that exhibit paramagnetic compounds, are compounds which have unpaired electrons. The Table below shows some examples of paramagnetic compounds.

TABLE

Paramagnetic substances	
Paramagnetic metal ions Transition metals	Co^{2+}, Mn^{2+}, Cu^{2+}, Cr^{3+}, Fe^{2+}, Fe^{3+}
Lanthanides	Eu^{3+}, Gd^{3+}, Dy^{3+}, Ho^{3+}
Paramagnetic chelates*	MnEDTA, GdEDTA, MnDTPA, CoEDTA, CrDTPA, FeNTA
Stable free radicals	nitroxides
Molecules with unpaired electrons	O_2, NO, NO_2

*NTA = Nitrilo triacetic acid
EDTA = Ethylene diamine tetraacetic acid
DTPA = Diethylene triamine pentaacetic acid

Molecular oxygen has been used as a vascular paramagnetic contrast agent, but molecules such as NO and NO_2 are too toxic to be used in NMR imaging. Nitroxides however have been proposed as renal NMR contrast agents by Brasch *et al* in Radiology *147* (1983) 773.

Paramagnetic metals and chelates are now the most frequently used contrast agents in experimental NMR imaging. Manganese chloride ($MnCl_2$) has been used as an NMR contrast agent in animal studies, but the salt is probably too toxic for use in *in vivo* human experiments. Other paramagnetic ions such as Gd^{3+}, Dy^{3+}, Ho^{3+}, Fe^{3+} and Cr^{3+} have also been used in *in vitro* or in *in vivo* NMR experiments.

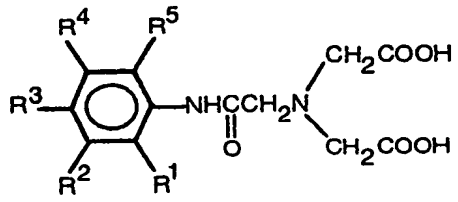
Schering AG in EP—A—71564 and EP—A—130934 describe the preparation and use in NMR imaging of salts of paramagnetic chelates such as MnEDTA, DyEDTA, HoEDTA, GdDTPA, and GdDOTA (DOTA = 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid). Stable EDTA and DTPA chelates are excreted in the urine and thus are potential parenteral NMR contrast agents for the enhancement of renal structures.

Paramagnetic chelates with desferrioxamine B, glucoheptonic acid and inositol hexaphosphoric acid have also been used as renal contrast agents in NMR imaging. A selective decrease in relaxation times of infarcted myocardium with the use of manganese-labelled monoclonal antibody has been shown.

Various particulate paramagnetic compounds have been studied for reticuloendothelial enhancement in NMR imaging of the liver, the particulate material being trapped in the reticuloendothelial system. We are unaware however that as yet any soluble paramagnetic chelates have been described as a parenterally administrable NMR contrast agent concentrating in the liver or the bile.

We have now found the certain soluble anilide-based paramagnetic chelates can be administered orally or parenterally, e.g. by intravenous injection, to achieve a contrast effect in NMR imaging, e.g. of the liver and the bile.

In one aspect, the invention thus provides an NMR contrast agent comprising at least one water-soluble, non-radioactive paramagnetic metal chelate together with at least one physiologically acceptable carrier or excipient, characterised in that said chelate is a chelate with a chelating agent of formula I



(I)

(wherein R^1 to R^5, which may be the same or different, each represent hydrogen or halogen atoms, optionally halogenated alkyl or alkoxy groups or carboxyl groups) or a physiologically acceptable salt thereof.

The chelates in the contrast agent of the invention preferably have high lipophilicity and particularly preferably are complexes or a paramagnetic lanthanide or transition metal.

In the chelating entity, R^1 to R^5 are conveniently optionally halogenated lower (C_{1-4}) alkyl or alkoxy groups but preferably are hydrogen, fluorine, lower (i.e. C_{1-4}) alkyl, or fluorinated lower alkyl (e.g. CF_3). Particularly preferably R^1 to R^5 are fluorine, or R^1, R^3 and R^5 are hydrogen and R^2 and R^4 are —CF_3, or R^1 and R^5 are lower alkyl and R^2 to R^4 are hydrogen.

We have found that the contrast agents of the invention are particularly effective as hepatobiliary contrast agents when the paramagnetic metal in the chelate is a trivalent cation, especially preferably Cr^{3+}, Fe^{3+} or Gd^{3+}.

The chelates of the non-radioactive paramagnetic metals with compounds of formula I or salts thereof are novel and thus in a further aspect the invention provides a water-soluble, non-radioactive paramagnetic chelate, for example of chromium or gadolinium, characterised in that the chelating entity thereof is a compound of formula I or a physiologically acceptable salt thereof.

The chromium (III) chelate of N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid and its salts are particularly preferred.

Certain chelating agents of formula I are known and their chelates with ^{99m}Tc have been used as cholescintigraphic agents. These "technetium chelates" are described for example by Nunn *et al* in J. Nucl. Med *24* (1983) 423, by Loberg *et al* in J. Nucl. Med. *17* (1976) 633, by E. R. Squibb & Sons Inc in GB—A—2090252 and by Hoescht AG in EP—A—12967 and are found to possess low renal secretion, high hepatobiliary specificity and rapid hepatocellular transit times.

Certain of the chelating agents of formula I however are novel and thus in another aspect the invention provides N-[3,5-bis(trifluoromethyl)phenylcarbamoylmethyl]iminodiacetic acid and the physiologically acceptable salts thereof. This novel compound may be prepared by reacting disodium iminodiacetic acid with ω-chloro-3,5-bis(trifluoromethyl)acetanilide, and its salts may be prepared in conventional ways from the free acid and a physiologically acceptable base.

In a still further aspect, the invention provides a process for the preparation of an NMR contrast agent according to the invention, which process comprises admixing in aqueous solution a chelating agent in formula I or a physiologically acceptable non-radioactive salt thereof and an at least sparingly soluble paramagnetic metal compound, e.g. a water-soluble paramagnetic metal salt the counterion whereof is physiologically acceptable or an at least sparingly soluble oxide or carbonate, optionally in suspension.

In a yet further aspect the invention provides a process for the preparation of a water-soluble non-radioactive paramagnetic chelate according to the invention, which process comprises admixing in aqueous solution a chelating agent of formula I or a physiologically acceptable salt thereof and an at least sparingly water soluble non-radioactive paramagnetic metal compound, e.g. a water-soluble paramagnetic metal salt the counterion whereof is physiologically acceptable or an at least sparingly soluble oxide or carbonate, optionally in suspension.

Where chelate formation is by reaction of a compound of formula I with a trivalent paramagnetic ion, this is preferably achieved by reaction of one equivalent of the paramagnetic metal with two equivalents of the chelating entity.

The contrast agents of the invention may be pre-formed or may alternatively be prepared directly before administration by mixing in aqueous solution the chelating agent and a soluble compound containing the paramagnetic metal e.g. in salt form with a physiologically acceptable counter ion, for example a halide, such as chloride. Where the chelating entity is itself in salt form the counter ion should also be physiologically acceptable and may for example be meglumine or an alkali metal ion such as sodium. With the chelating agents of formula I, chelate formation appears to happen within a few seconds at from ambient temperature to the boiling temperature of the solution.

Thus in another aspect the invention provides a kit comprising a water-soluble non-radioactive paramagnetic metal compound, e.g. a Gd^{3+}, Cr^{3+} or Fe^{3+} compound, and chelating agent of formula I or a physiologically acceptable salt thereof; either or both being optionally in solution in a physiologically acceptable carrier solvent, e.g. water for injections.

Where the contrast agent of the invention is supplied in the form of a solution of the paramagnetic chelate in a physiologically acceptable carrier solvent, e.g. water for injections, the solution may be in concentrated form for dilution before administration.

As it is preferred that the contrast agent of the invention be at physiological pH, it may also contain a buffer.

Administration of the contrast agents of the invention is preferably by intravenous injection of solutions containing the paramagnetic chleate in sufficient concentration to provide the desired hepatobiliary NMR-contrast effect. In this respect solutions containing the paramagnetic metal in concentrations of from 0.1 to 200 mM are suitable. Alternatively the contrast agents are formulated in forms suitable for oral administration, e.g. solutions, tablets or capsules.

The contrast agents may conveniently be administered in amounts of from 10^{-4} to 10^{-1} mmol paramagnetic metal/kg bodyweight.

An NMR image suitable for use in diagnosis may be generated by a method which comprises administering an NMR contrast agent of the invention to a human or animal subject and generating an NMR image of at least a part of said subject in which said contrast agent is present.

A preferred embodiment of this method comprises NMR imaging wherein hepatobiliary contrast enhancement is achieved by administering an effective amount of at least one chelate of a paramagnetic metal (preferably Cr^{3+}, Fe^{3+}, Gd^{3+}) with a chelating agent of formula I or a salt thereof intravenously to a human or animal subject and generating an NMR image of the liver and/or biliary system of said subject.

In a yet further aspect, the invention thus provides the use of a water-soluble non-radioactive paramagnetic metal chelate wherein the chelating entity is a compound of formula I or a physiologically acceptable salt thereof for the manufacture of a diagnostic agent for use in diagnosis of the human or animal body using NMR imaging.

Our experiments have shown chelates according to the invention to be efficient relaxation agents *in vitro* and to have high hepatobiliary specificity and rapid hepatocellular transit times. Thus in a rabbit, after intravenous injection of 0.0075 mmol gadolinium/kg bodyweight in the form of a chelate with a compound of formula I in which the phenyl moiety is a 2,6-dimethyl-phenyl group, the contrast enhancement of the liver and the intestine 15 minutes after injection was very good. At this time the contrast agent had started to excrete from the liver. The chelate did not, however, show any contrast enhancement of the kidneys.

The rabbit was killed 1 hour after the injection, and the relaxation times in the liver and the kidneys were measured. The relaxation times in these organs were normal, which shows that all of the chelates had left the liver during the first hour. The quality of the NMR picture obtained with this chelate was much better than the general standard of NMR pictures published in the literature.

The contrast agents and chelates of the invention will now be illustrated further by the following non-limiting Examples:

Intermediate 1

N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid

The *title compound* was prepared from ω-chloro-2,6-dimethylacetanilide and iminodiacetic acid by the procedure described by Callery *et al.* in J. Med. Chem. *19* (1976) 962. The product was isolated in 75% yield following reflux of the mixture for 3 hours; m.p. 216—217°C

Intermediate 2

N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid

The *title compound* was prepared from ω-chloro-2,6-diethylacetanilide and iminodiacetic acid in a manner analogous to the preparation of Intermediate 1. The mixture was refluxed for 5 hours; yield 75%; m.p. 187—188°C.

Intermediate 3

N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid

The *title compound* was prepared from ω-chloro-2,4,6-trimethylacetanilide and iminodiacetic acid in a manner analogous to the preparation of Intermediate 1. The mixture was refluxed for 4½ hours; yield 79%; m.p. 220—221°C.

Intermediate 4

N-(2,3,4,5,6-pentafluorophenylcarbamoylmethyl)iminodiacetic acid

The *title compound* was prepared from ω-chloro-2,3,4,5,6-pentafluoroacetanilide and iminodiacetic acid in a manner analogous to the preparation of Intermediate 1. The mixture was refluxed for 1 hour; yield 78%; m.p. 182—183°C.

Example 1

N-[3,5-Bis(trifluoromethyl)phenylcarbamoylmethyl]iminodiacetic acid

Chloroacetyl chloride (17.8 g = 157.5 mmol) was added dropwise to a solution of 3,5-bis(trifluoromethyl)aniline (34.4 g = 150 mmol) and triethylamine (15.2 g = 150 mmol) in toluene (300 ml) under cooling on ice. The temperature was slowly adjusted to ambient temperature and the reaction mixture was stirred for 1½ hours. Toluene was removed by distillation and the oily residue was washed with H_2O (300 ml). The oily residue was suspended in H_2O (300 ml) and placed in the refrigerator overnight. The precipitate was isolated by filtration and dissolved in boiling n-hexane (400 ml). The solution was filtered

and cooled to ambient temperature. The crystals of ω-chloro-3,5-bis(trifluoromethyl)acetanilide were isolated by filtration. Yield 80%; m.p. 87—88°C.

Disodium iminodiacetic acid (37.2 g = 210 mmol) and ω-chloro-3,5-bis(trifluoromethyl)acetanilide (30.6 g = 100 mmol) were dissolved in a solution of ethanol-water (50:50) at 80°C. After 5 hours the ethanol was removed by distillation and the residue was extracted with diethylether (3 × 60 ml). The ether was removed by distillation and the pH was adjusted to 2. The precipitate was filtered off and washed with dilute HCl (200 ml), dissolved in boiling ethanol (400 ml) and precipitated with H_2O (750 ml). The *title compound* was isolated by filtration. Yield 22.2 g (55%); m.p. 201°C. ^{1}H—NMR(DMSO-d_6): δ 3.77 (s; —CH_2—), 7.27 and 8.37 (Ph), 11.20 (s; COOH), 11.54 (broad s, —NH—). ^{13}C—NMR (DMSO-d_6): δ 56.0 (—CH_2—), 59.1 (—CH_2—), 105.3—141.6 (Ph and —CF_3),

Calculated (for $C_{14}H_{12}F_6N_2O_5$): C 41.80, H 3.01, N 6.96, F 28.34
Found: C 41.87, H 3.23, N 7.30, F 28.20

General procedure for formation of a gadolinium (III)-, iron (III)- and chromium (III) chelate with Intermediates 1 to 4 and Example 1

An aqueous solution of the disodium salt of the chelating agent (1 equivalent) and the metal (III) chloride hexahydrate (2 equivalents) was stirred and refluxed for one hour. The stirring was continued for one hour at ambient temperature. The pH was adjusted to 1.5 with dilute HCl and the metal chelate was isolated by filtration.

General procedure for formation of a manganese (II)-, copper (II), cobalt (II)-, and nickel (II) chelate with Intermediates 1 to 4 and Example 1

An aqueous solution of the disodium salt of the chelating agent (1 equivalent) and the hydrated metal (II) chloride (1 equivalent) was stirred and heated to boiling. After cooling to ambient temperature the stirring was continued for one hour. The metal chelate was isolated by filtration.

Example 2

Gadolinium (III) chelate of N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 72.2%, M.p. >350°C. Solubility as sodium salt in water: >0.02 M.

Analysis: $C_{28}H_{32}N_4O_{10}GdNa$.
Calculated: C 43.96, H 4.21, N 7.32, Gd 20.56, Na 2.73
Found: C 43.76, H 4.38, N 7.16, Gd 20.30, Na 2.70

Specific relaxation rate enhancement (SRRE) was measured in a NMR proton spin analyzer (RADX Corp., Houston, Texas, USA) at 10 MHz in glycerol:water 1:2 (v:v) at 37°C: 5.22 s^{-1} mM^{-1}:

Example 3

Gadolinium (III) chelate of N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 63%. M.p.: >350°C. Solubility as sodium salt in water: >0.1 M.

Example 4

Gadolinium (III) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 66%. M.p.: >350°C. Solubility as sodium salt in water: >0.1 M.

Example 5

Gadolinium (III) chelate of N-(2,3,4,5,6-pentafluorophenylcarbamoylmethyl)iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 43%. M.p.: >350°C. Solubility as sodium salt in water: >0.1 M.

Example 6

Gadolinium (III) chelate of N-[3,5-bis(trifluoromethyl)-phenylcarbamoylmethyl)iminodiacetic acid

The gadolinium (III) chelate was isolated from a 0.15 M solution as white crystals. Yield: 79%. M.p.: >350°C. Solubility as sodium salt in water: >0.1 M.

Example 7

Iron (III) chelate of N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid

The iron (III) chelate was isolated as light yellow powder. Yield: 85%. M.p.: 220°C (decomp).

Analysis: $C_{28}H_{33}N_4O_{10}Fe$
Calculated: C 52.43, H 5.19, N 8.74, Fe 8.71
Found: C 51.59, H 5.23, N 8.63, Fe 8.71
SRRE: 1.86 s^{-1} mM^{-1}

Preparation of the meglumine salt of the iron (III) chelte of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

The iron (III) chelate of N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid (160 mg = 0.25 mmol) was dissolved in methanol (20 ml) and N-methylglucamine (49 mg = 0.25 mmol) was added over a period of 15 minutes. The solution was evaporated to dryness and the meglumine salt of the iron (III) chelate of N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid was isolated as yellow crystals in a quantitative yield.

Example 8

Iron (III) chelate of N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid

The iron (III) chelate was isolated from a 0.14 M solution as a light yellow powder. Yield: 63%. M.p.: 250°C (decomp).

Example 9

Iron (III) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid

The iron (III) chelate was isolated from a 0.04 M solution as a light yellow powder. Yield: 88%. M.p.: 200°C (decomp).

Example 10

Iron (III) chelate of N-[3,5-bis(trifluoromethyl)phenylcarbamoyl-methyl)]iminodiacetic acid

The iron (III) chelate was isolated from a 0.04 M solution as a light yellow powder. Yield: 78%. M.p.: 200°C (decomp).

Example 11

Chromium (III) chelate of N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid

The chromium (III) chelate was isolated from a 0.03 M solution as grey powder. Yield: 68%. M.p.: >320°C.

The meglumine salt of the complex was prepared in the same way as described in Example 12 (A).

Analysis: $C_{35}H_{50}N_5O_{15}Cr$

Calculated:	C 50.48,	H 6.05,	N 8.41,	Cr 6.24
Found:	C 50.68,	H 5.28,	N 7.38,	Cr 6.81

Example 12

Chromium (III) chelate of N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid and its meglumine salt

The chromium (III) chelate was isolated from 0.14 M solution as grey powder. Yield: 71%. M.p.: >320°C.

(A) Preparation of the meglumine salt of the chromium (III) chelate of N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid

To a solution of the chromium (III) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid (140 mg = 0.2 mmol) in methanol (38 ml) was added N-methylglucamine (39 mg = 0.2 mmol) over a period of 15 minutes. The solution was evaporated to dryness and the meglumine salt of the complex was isolated as a pink powder in a quantitative yield. M.p.: >320°C. Relaxation time (T_1) of a 10 mM solution of the product in water was 158 msec. T_1 (pure water): 3300 msec.

(B) Preparation of chromium (III) chelate of N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid and its meglumine salt

N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid (1.29 g = 4 mmol) and freshly prepared $Cr(OH)_3$ (206 mg = 2 mmol) was suspended in H_2O (250 ml). N-methylglucamine (390 mg = 2 mmol) was added in small portions while the suspension was stirred and heated at 95°C for 48 hours. The pink reaction mixture was filtered and evaporated to dryness. The meglumine salt of chromium (III) — N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid was isolated in 98% yield as pink powder.

Example 13

Chromium (III) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid

The chromium (III) chelate was isolated from a 0.28 M solution as grey powder. Yield: 63%. M.p.: >320°C.

Example 14

Cobalt (II) chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

The cobalt (II) chelate was isolated from a 0.2 M solution as a pink powder. Yield: 59%, M.p.: >300°C. T_1 (10 mM; H_2O): 698 msec.

Example 15

Cobalt (II) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid

The cobalt (II) chelate was isolated from a 0.27 M solution as a pink powder. Yield: 90%. M.p.: >300°C.

Analysis: $C_{16}H_{20}N_2O_5Co$

Calculated:	C 50.67,	H 5.31,	N 7.39,	Co 15.54
Found:	C 50.70,	H 5.54,	N 7.00,	Co 14.90

Example 16

Cobalt (II) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl) iminodiacetic acid

The cobalt (II) chelate was isolated from a 0.11 M solution as a pink powder. Yield: 86%. M.p.: >300°C.

Example 17

Cobalt (II) chelate of N-[3,5-bis(trifluoromethyl)phenylcarbamoylmethyl)] iminodiacetic acid

The cobalt (II) chelate was isolated from a 0.18 M solution as a pink powder. Yield: 87%. M.p.: >300°C.

Example 18

Copper (II) chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

The copper (II) chelate was isolated as a light blue powder. Yield: 76%. M.p.: 270°C dcomp).

Analysis: $C_{14}H_{16}N_2O_5Cu$

Calculated: C 47.26, H 4.53, N 7.87, Cu 17.86

Found: C 47.35, H 4.63, N 7.47, Cu 17.04

Example 19

Copper (II) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid

The copper (II) chelate was isolated from a 0.27 M solution as a light blue powder. Yield: 63%. M.p.: 250°C (decomp).

Example 20

Copper (II) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl) iminodiacetic acid

The copper (II) chelate was isolated from a 0.11 M solution as a light blue powder. Yield: 62%. M.p.: 250°C (decomp).

Example 21

Manganese (II) chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

The manganese (II) chelate was isolated from a 0.27 M solution as a white powder. Yield: 57%. M.p.: >350°C.

Example 22

Manganese (II) chelate of N-(2,6-diethylphenylcarbamoylmethyl)iminodiacetic acid

The manganese (II) chelate was isolated from a 0.32 M solution as a white powder. Yield: 80%. M.p.: >350°C.

Analysis: $C_{16}H_{20}N_2O_5Mn$

Calculated: C 51.21, H 5.37, N 7.46, Mn 14.64

Found: C 51.80, H 5.69, N 7.27, Mn 14.90

Example 23

Manganese (II) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl) iminodiacetic acid

The manganese (II) chelate was isolated from a 0.36 M solution as a white powder. Yield: 62%. M.p.: >350°C.

Example 24

Manganese (II) chelate of N-(2,3,4,5,6-pentafluorophenylcarbamoylmethyl) iminodiacetic acid

The manganese (II) chelate was isolated from a 0.24 M solution as a white powder. Yield: 47%. M.p.: >350°C.

Analysis: $C_{12}H_7F_5N_2O_5Mn$

Calculated: C 35.23, H 1.72, N 6.85, Mn 13.4

Found: C 35.18, H 1.97, N 6.53, Mn 12.9

Example 25

Manganese (II) chelate of N-[3,5-bis(trifluoromethyl)phenylcarbamoylmethyl)] iminodiacetic acid

The manganese (II) chelate was isolated from a 0.18 M solution as a white powder. Yield: 82%. M.p.: >350°C.

Example 26

Nickel (II) chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

The nickel (II) chelate was isolated as a light green powder. Yield: 30%. M.p.: >300°C. T_1 (10 mM; H_2O): 311 msec.

Example 27

Nickel (II) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid

The nickel (II) chelate was isolated from a 0.27 M solution as a light green powder. Yield: 42%. M.p.: >300°C.

Example 28

Nickel (II) chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl) iminodiacetic acid

The nickel (II) chelate was isolated from a 0.11 M solution as a light green powder. Yield: 38%. M.p.: >300°C.

Example 29

Nickel (II) chelate of N-[3,5-bis(trifluoromethyl)phenylcarbamoylmethyl)] iminodiacetic acid

The nickel (II) chelate was isolated from a 0.09 M solution as a light green powder. Yield: 87%. M.p.: >300°C.

Preparation of solutions for NMR imaging form isolated chelates

Example 30

Manganese chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

An autoclaved isotonic 30 mM solution of the manganese chelate of N-(2,6-dimethylcarbamoylmethyl)iminodiacetic acid in a 10 ml vial was prepared from:

Chelate of Example 21	104 mg
Sodium chloride	81 mg
Aqua purificata	*ad* 10 ml

Example 31

Gadolinium chelate of N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid

An autoclaved isotonic 13 mM solution of the sodium salt of the gadolinium chelate of N-(2,6-dimethylcarbamoylmethyl) iminodiacetic acid in a 10 ml vial was prepared from:

Sodium salt of the chelate of Example 2	100 mg
Sodium chloride	84 mg
Aqua purificata	*ad* 10 ml

Example 32

Preparation of capsules for oral use

Chromium (III) chelate of N-(2,6-diethylphenylcarbamoylmethyl) iminodiacetic acid (Example 12)	306.4 mg
Amylum maydis	q.s.

The powder was mixed and filled in capsules. (Capsule size 0.) Each capsule contained 25 mg chromium.

Preparation of solutions for NMR imaging in situ:

Example 33

Manganese chleate of N-(2,3,4,5,6-pentafluorophenylcarbamoylmethyl) iminodiacetic acid

Solution A

An autoclaved isotonic 28 mM solution of the disodium salt of N-(2,3,4,5,6-pentafluorophenylcarbamoylmethyl)iminodiacetic acid in a 20 ml vial was prepared from:

N-(2,3,4,5,6-pentafluorophenyl carbamoylmethyl) iminodiacetic acid	100 mg
Sodium hydroxide	2 equivalents*
Sodium chloride	68 mg
Aqua purificata	*ad* 10 ml

*(i.e. 2 equivalents of the N-(2,3,4,5,6-pentafluorophenylcarbamoylmethyl) iminodiacetic acid)

Solution B

An autoclaved isotonic 25 mM solution of manganese chloride in a 10 ml vial was prepared from:

Manganese chloride (36.8% H_2O)	50 mg
Sodium chloride	69 mg
Aqua purificata	*ad* 10 ml

The chelate was prepared by adding solution B to solution A. After mixing, the solution is ready for use.

Example 34

Gadolinium chelate of N-(2,4,6-trimethylphenylcarbamoylmethyl) iminodiacetic acid

Solution A

An autoclaved 60 mM isotonic solution of the disodium salt of N-(2,4,6-trimethylphenylcarbamoylmethyl) iminodiacetic acid in a 20 ml vial was prepared from:

N-2,4,6-trimethylphenylcarbamoylmethyl) imidoacetic acid	228 mg
Sodium hydroxide	2 equivalents
Sodium chloride	36 mg
Aqua purificata	*ad* 10 ml

Solution B

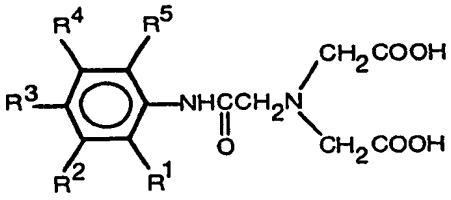
An autoclaved isotonic 25 mM solution of gadolinium chloride in a 10 ml vial was prepared from:

Gadolinium chloride (35.9% H_2O)	66 mg
Sodium chloride	69 mg
Aqua purificata	*ad* 10 ml

The chelate was prepared by adding solution B to solution A. After mixing, the solution is ready for use.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. An NMR contrast agent comprising at least one water-soluble, non-radioactive paramagnetic metal chelate together with at least one physiologically acceptable carrier or excipient, characterised in that said chelate is a chelate with a chelating agent of formula I



(I)

(wherein R^1 to R^5, which may be the same or different, each represent hydrogen or halogen atoms, optionally halogenated alkyl or alkoxy groups or carboxyl groups) or a physiologically acceptable salt thereof.

2. A contrast agent as claimed in claim 1 comprising from 0.1 to 200mM of said paramagnetic metal in aqueous solution.

3. A contrast agent as claimed in either one of claims 1 and 2 wherein said chelate is a chelate of a trivalent metal ion.

4. A contrast agent as claimed in claim 3 wherein said chelate is a chelate of Fe^{3+}.

5. A contrast agent as claimed in claim 3 wherein said chelate is a chelate of Gd^{3+}.

6. A contrast agent as claimed in claim 3 wherein said chelate is a chelate of Cr^{3+}.

7. A contrast agent as claimed in claim 6 wherein said chelate is a chelate with the chelating agent N-(2,6-diethylphenyl-carbamoyl-methyl)iminodiacetic acid or a physiologically acceptable salt thereof.

8. A contrast agent as claimed in claim 6 wherein said chelate is (a) the chromium (III) chelate of N-(2,6-diethylphenyl-carbamoylmethyl)iminodiacetic acid; (b) the chromium (III) chelate of the meglumine salt of N-(2,6-diethylphenyl-carbamoylmethyl)iminodiacetic acid; (c) the chromium (III) chelate of N-(2,6-dimethylphenyl-carbamoylmethyl)iminodiacetic acid; or (d) the chromium (III) chelate of N-(2,4,6-trimethylphenyl-carbamoylmethyl)-iminodiacetic acid.

9. A contrast agent as claimed in claim 1 wherein said chelate is a chelate with a chelating agent of formula I (as defined in claim 1 and wherein R^1 to R^5 are fluorine atoms, or R^1, R^3 and R^5 are hydrogen atoms and R^2 and R^4 are trifluoromethyl groups, or R^1 and R^5 are C_{1-4} alkyl groups and R^2 to R^4 are hydrogen atoms) or a physiologically acceptable salt thereof.

10. A water-soluble non-radioactive paramagnetic chelate characterised in that the chelating entity thereof is a compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof.

11. A chelate as claimed in claim 10 being a chelate of a trivalent paramagnetic metal ion.

12. A chelate as claimed in claim 11 wherein said metal ion is Fe^{3+}.

13. A chelate as claimed in claim 11 wherein said metal ion is Gd^{3+}.

14. A chelate as claimed in claim 11 wherein said metal ion is Cr^{3+}.

15. A chelate as claimed in claim 14 wherein said chelating entity is N-(2,6-diethylphenyl-carbamoylmethyl)iminodiacetic acid or a physiologically acceptable salt thereof.

16. A chelate as claimed in claim 10 being (a) the chromium (III) chelate of N-(2,6-diethylphenyl-carbamoylmethyl)iminodiacetic acid; (b) the chromium (III) chelate of the meglumine salt of N-(2,6-diethyl-

phenyl-carbamoylmethyl)iminodiacetic acid; (c) the chromium (III) chelte of N-(2,6-dimethylphenyl-carbamoylmethyl)iminodiacetic acid; or (d) the chromium (III) chelate of N-(2,4,6-trimethylphenyl-carbamoylmethyl)-iminodiacetic acid.

17. A chelate as claimed in claim 10 wherein in said chelating compound of formula I R^1 to R^5 are fluorine atoms, or R^1, R^3 and R^5 are hydrogen atoms and R^2 and R^4 are trifluoromethyl groups, or R^1 and R^5 are C_{1-4} alkyl groups and R^2 to R^4 are hydrogen atoms.

18. N-(3,5-Bis(trifluoromethyl)phenylcarbamoylmethyl]iminodiacetic acid and physiologically acceptable salts thereof.

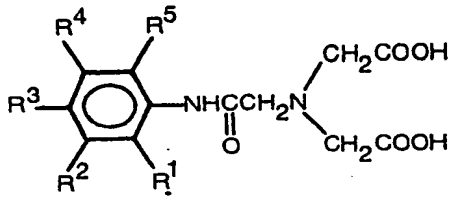
19. The use of a chelate as defined in claim 1 for the manufacture of a diagnostic agent for use in diagnosis of the human or animal body using NMR imaging.

20. A process for the preparation of an NMR contrast agent which process comprises admixing in aqueous solution a chelating agent of formula I (as defined in claim 1) or a physiologically acceptable salt thereof and an at least sparingly water soluble non-radioactive paramagnetic metal compound.

21. A process for the preparation of a water-soluble non-radioactive paramagnetic chelate which process comprises admixing in aqueous solution a chelating agent of formula I (as defined in claim 1) or a physiologically acceptable salt thereof with an at least sparingly water soluble non-radioactive paramagnetic metal compound.

Claims for the Contracting State: AT

1. A process for the preparation of an NMR contrast agent which process comprises admixing in aqueous solution an at least sparingly water-soluble non-radioactive paramagnetic metal metal compound and a chelating agent, characterised in that said chelating agent is a compound of formula I



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(wherein R^1 to R^5, which may be the same or different, each represent hydrogen or halogen atoms, optionally halogenated alkyl or alkoxy goups or carboxyl groups) or a physiologically acceptable salt thereof.

2. A process for the preparation of an NMR contrast agent which process comprises admixing with at least one physiologically acceptable carrier or excipient at least one water soluble non-radioactive paramagnetic chelate, characterised in that as said chelate is used a chelate with a chelating agent of formula I (as defined in claim 1) or with a physiologically acceptable salt thereof.

3. A process as claimed in either one of claims 1 and 2 wherein admixture is effected to yield a said contrast agent comprising from 0.1 to 200mM of said paramagnetic metal in aqueous solution.

4. A process as claimed in any one of claims 1 and 3 wherein the paramagnetic metal species in said paramagnetic metal chelate is a trivalent metal ion.

5. A process as claimed in claim 4 wherein said chelate is a chelate of Fe^{3+}.

6. A process as claimed in claim 4 wherein said chelate is a chelate of Gd^{3+}.

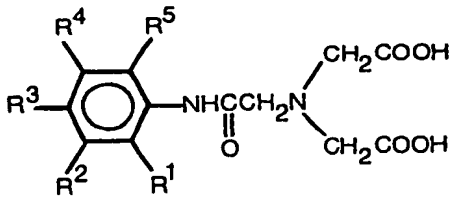
7. A process as claimed in claim 4 wherein said chelate is a chelate of Cr^{3+}.

8. A process as claimed in claim 7 wherein said chelating agent N-(2,6-diethylphenyl-carbamoyl-methyl)iminodiacetic acid or a physiologically acceptable salt thereof.

9. A process as claimed in claim 7 wherein said chelate is (a) the chromium (III) chelate of N-(2,6-diethylphenyl-carbamoylmethyl)iminodiacetic acid; (b) the chromium (III) chelate of the meglumine salt of N-(2,6-diethylphenyl-carbamoylmethyl)iminodiacetic acid; (c) the chromium (III) chelate of N-(2,6-dimethyl-phenyl-carbamoylmethyl)iminodiacetic acid; or (d) the chromium (III) chelate of N-(2,4,6-trimethylphenyl-carbamoylmethyl)-iminodiacetic acid.

10. A process as claimed in either one of claims 1 and 2 wherein said chelating agent is a compound of formula I wherein R^1 to R^5 are fluorine atoms, or R^1, R^3 and R^5 are hydrogen atoms and R^2 and R^4 are trifluoromethyl groups, or R^1 and R^5 are C_{1-4} alkyl groups and R^2 to R^4 are hydrogen atoms or a physiologically acceptable salt thereof.

11. An NMR contrast agent comprising at least one water-soluble, non-radioactive paramagnetic metal chelate together with at least one physiologically acceptable carrier or excipient, characterised in that said chelate is a chelate with a chelating agent of formula I



(I)

(wherein R^1 to R^5, which may be the same or different, each represent hydrogen or halogen atoms, optionally halogenated alkyl or alkoxy groups or carboxyl groups) or a physiologically acceptable salt thereof.

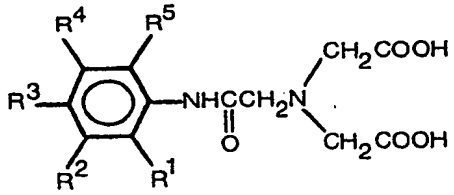
12. A process for the preparation of a water-soluble non-radioactive paramagnetic chelate which process comprises admixing in aqueous solution an at least sparingly water soluble non-radioactive paramagnetic metal compound and a chelating agent of formula I (as defined in claim 1) or a physiologically acceptable salt thereof.

13. A process for the preparation of N-[3,5-bis(trifluoromethyl)phenylcarbamoylmethyl]iminodiacetic acid or a physiologically acceptable salt thereof, said process comprising reacting disodium iminodiacetic acid with ω-chloro-3,5-bis(trifluoromethyl)acetanilide and optionally reacting the product so obtained with a physiologically acceptable base.

14. The use of a chelate as defined in claim 1 for the manufacture of a diagnostic agent for use in diagnosis of the human or animal body using NMR imaging.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. NMR-Kontrastmittel, welches wenigstens ein wasserlösliches, nicht-radioaktives paramagnetisches Metallchelat zusammen mit wenigstens einem physiologisch verträglichen Träger oder Excipienten umfassen, dadurch gekennzeichnet, daß das Chelat einen Chelatbildner der allgemeinen Formel (I)



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worin R^1 bis R^5 gleich oder verschiedenen sind und jeweils Wasserstoff-oder Halogenatome, gegebenenfalls halogenierte Alkyl- oder Alkoxygruppen oder Carboxygruppen bedeuten, oder ein physiologisch verträgliches Salz davon umfaßt.

2. Kontrastmittel nach Anspruch 1, das 0,1 bis 200 mM des paramagnetischen Metalls in wäßriger Lösung umfaßt.

3. Kontrastmittel nach einem der Ansprüche 1 und 2, wobei das Chelat ein Chelat eines trivalenten Metallions ist.

4. Kontrastmittel nach Anspruch 3, wobei das Chelat ein Chelat von Fe^{3+} ist.

5. Kontrastmittel nach Anspruch 3, wobei das Chelat ein Chelat von Gd^{3+} ist.

6. Kontrastmittel nach Anspruch 3, wobei das Chelat ein Chelat von Cr^{3+} ist.

7. Kontrastmittel nach Anspruch 6, wobei das Chelat als Chelatbildner N-(2,6-Diethylphenylcarbamoylmethyl)iminodiessigsäure oder ein physiologisch verträgliches Salz davon umfaßt.

8. Kontrastmittel nach Anspruch 6, wobei das Chelat (a) das Chrom-(III)-Chelat von N-(2,6-Diethylphenylcarbamoylmethyl)iminodiessigsäure; (b) das Chrom-(III)-Chelat des Megluminsalzes von N-(2,6-Diethylphenylcarbamoylmethyl)iminodiessigsäure; (c) das Chrom-(III)-Chelat von N-(2,6-Dimethylphenylcarbamoylmethyl)iminodiessigsäure; oder (d) das Chrom-(III)-Chelat von N-(2,4,6-Trimethyl)phenylcarbamoylmethyl)iminodiessigsäure ist.

9. Kontrastmittel nach Anspruch 1, wobei das Chelat einen Chelatbildner der allgemeinen Formel (I) gemäß Anspruch 1, worin R^1 bis R^5 Fluoratome bedeuten, oder R^1, R^3 und R^5 Wasserstoffatome bedeuten und R^2 und R^4 Trifluormethylgruppen bedeuten, oder R^1 und R^5 C_{1-4}-Alkylgruppen und R^2 bis R^4 Wasserstoffatome bedeuten) oder ein physiologisch verträgliches Salz davon umfaßt.

10. Wasserlösliches nicht-radioaktives paramagnetisches Chelat, dadurch gekennzeichnet, daß die Chelat bildende Einheit eine Verbindung der allgemeinen Formel (I) entsprechend der Definition nach Anspruch 1 oder ein physiologisch verträgliches Salz davon ist.

11. Chelat nach Anspruch 10, welches ein Chelat eines trivalenten paramagnetischen Metallions ist.

12. Chelat nach Anspruch 11, wobei das Metallion Fe^{3+} ist.

13. Chelat nach Anspruch 11, wobei das Metallion Gd^{3+} ist.

14. Chelat nach Anspruch 11, wobei das Metallion Cr^{3+} ist.

15. Chelat nach Anspruch 14, wobei die Chelat bildende Einheit N-(2,6-Diethylphenylcarbamoylmethyl)iminodiessigsäure oder ein physiologisch verträgliches Salz davon ist.

16. Chelat nach Anspruch 10, welches (a) das Chrom-(III)-Chelat von N-(2,6-Diethylphenylcarbamoylmethyl)iminodiessigsäure; (b) das Chrom-(III)-Chelat des Meglumінsalzes von N-(2,6-Diethylphenylcarbamoylmethyl)iminodiessigsäure; (c) das Chrom-(III)-Chelat von N-(2,6-Dimethylphenylcarbamoylmethyl)-iminodiessigsaure; oder (d) das Chrom-(III)-Chelat von N-(2,4,6-Trimethylphenylcarbamoylmethyl)-iminodiessigsäure ist.

17. Chelat nach Anspruch 10, wobei in der Chelat bildenden Verbindung der Formel (I) R^1 bis R^5 Fluoratome bedeuten, oder R^1, R^3 und R^5 Wasserstoffatome und R^2 und R^4 Trifluormethylgruppen bedeuten, oder R^1 und R^5 C_{1-4}-Alkylgruppen und R^2 bis R^4 Wasserstoffatome bedeuten.

18. N-(3,5-Bis(trifluormethyl)phenylcarbamoylmethyl)iminodiessigsäure und physiologisch verträgliche Salze davon.

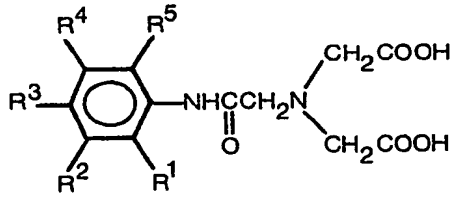
19. Verwendung eines Chelates nach Anspruch 1 zur Herstellung eines diagnostischen Mittels für die Verwendung bei der Diagnose des menschlichen oder tierischen Körpers mit Hilfe von NMR-Imaging.

20. Verfahren zur Herstellung eines NMR-Kontrastmittels, wobei das Verfahren das Vermischen eines Chelatbildners der allgemeinen Formel (I) gemäß der Definition in Anspruch 1 oder eines physiologisch verträglichen Salzes davon und einer zumindest geringfügig wasserlöslichen nicht-radioaktiven paramagnetischen Metallverbindung in wäßriger Lösung umfaßt.

21. Verfahren zur Herstellung eines wasserlöslichen nichtradioaktiven paramagnetischen Chelates, wobei das Verfahren das Vermischen eines Chelatbildners der allgemeinen Formel (I) gemäß der Definition in Anspruch 1 oder eines physiologisch verträglichen Salze davon und einer zumindest geringfügig wasserlöslichen nicht radioaktiven paramagnetischen Metallverbindung in wäßriger Lösung umfaßt.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines NMR-Kontrastmittels, wobei das Verfahren das Vermischen einer zumindest geringfügig wasserlöslichen nicht-radioaktiven paramagnetischen Metallverbindung und eines Chelatbildners in einer wäßrigen Lösung umfaßt, dadurch gekennzeichnet, daß der Chelatbildner eine Verbindung der allgemeinen Formel (I)



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worin R^1 bis R^5 gleich oder verschieden sind und jeweils Wasserstoff oder Halogenatome, gegebenenfalls halogenierte Alkyl- oder Alkoxygruppen oder Carboxygruppen bedeuten, oder ein physiologisch verträgliches Salz davon ist.

2. Verfahren zur Herstellung eines NMR-Kontrastmittels, wobei das Verfahren das Vermischen wenigstens eines wasserlöslichen nicht-radioaktiven paramagnetischen Chelates mit wenigstens einem physiologisch verträglichen Träger oder Excipienten umfaßt, dadurch gekennzeichnet, daß man ein Chelat mit einem Chelatbildner der allgemeinen Formel (I) entsprechend der Definition in Anspruch 1 oder einem physiologisch verträglichen Salz davon verwendet.

3. Verfahren nach einem der Ansprüche 1 und 2, wobei man durch Vermischen ein Kontrastmittel erhält, welches 0,1 bis 200 mM des paramagnetischen Metalls in wäßriger Lösung umfaßt.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei die paramagnetische Verbindung in diesem paramagnetischen Metallchelat ein trivalentes Metallion ist.

5. Verfahren nach Anspruch 4, wobei das Chelat ein Chelat von Fe^{3+} ist.

6. Verfahren nach Anspruch 4, wobei das Chelat ein Chelat von Gd^{3+} ist.

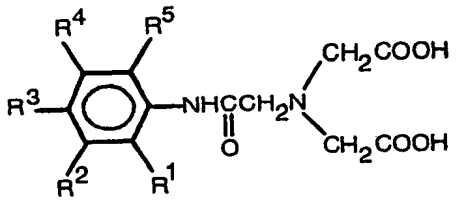
7. Verfahren nach Anspruch 4, wobei das Chelat ein Chelat von Cr^{3+} ist.

8. Verfahren nach Anspruch 7, wobei der Chelatbildner N-(2,6-Diethylphenylcarbamoylmethyl)-iminodiessigsäure oder ein physiologisch verträgliches Salz davon ist.

9. Verfahren nach Anspruch 7, wobei das Chelat (a) das Chrom-(III)-Chelat von N-(2,6-Diethylphenylcarbamoylmethyl)iminodiessigsäure; (b) das Chrom-(III)-Chelat des Meglumінsalz von N-(2,6-Diethylphenylcarbamoylmethyl)iminodiessigsäure; (c) das Chrom-(III)-Chelat von N-(2,6-Dimethylphenylcarbamoylmethyl)iminodiessigsäure; oder (d) das Chrom-(III)-Chelat von N-(2,4,6-Trimethylphenylcarbamoylmethyl)iminodiessigsäure ist.

10. Verfahren nach einem der Ansprüche 1 bis 2, wobei der Chelatbildner eine Verbindung der allgemeinen Formel (I), worin R^1 bis R^5 Fluoratome bedeuten, oder R^1, R^3 und R^5 Wasserstoffatome und R^2 und R^4 Trifluormethylgruppen bedeuten oder R^1 und R^5 für C_{1-4}-Alkylgruppen und R^2 bis R^4 für Wasserstoffatome stehen oder ein physiologisch verträgliches Salz davon ist.

11. NMR-Kontrastmittel, welches wenigstens ein wasserlösliches, nicht-radioaktives paramagnetisches Metallchelat zusammen mit wenigstens einem physiologisch verträglichen Träger oder Excipienten umfaßt, dadurch gekennzeichnet, daß das Chelat einen Chelatbildner der allgemeinen Formel (I)



(I)

worin R^1 bis R^5 gleich oder verschieden sind und jeweils Wasserstoff oder Halogenatome, gegebenenfalls halogenierte Alkyl-, Alkoxy- oder Carboxygruppen bedeuten oder ein physiologisch verträgliches Salz davon ist.

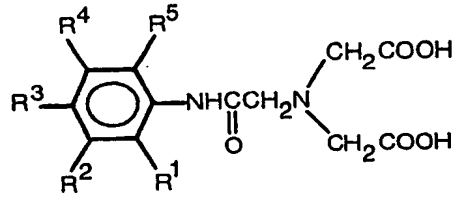
12. Verfahren zur Herstellung eines wasserlöslichen nicht-radioaktiven paramagnetischen Chelates, wobei das Verfahren das Vermischen einer wenigstens geringfügig wasserlöslichen nicht-radioaktiven p-magnetischen Metallverbindung und eines Chelatbildners der allgemeinen Formel (I) entsprechend der Definition in Anspruch 1 oder eines physiologisch verträglichen Salzes davon in einer wäßrigen Lösung umfaßt.

13. Verfahren zur Herstellung von N-[3,5-bis(Trifluormethyl)phenylcarbamoylmethyl)iminodiessigsäure oder einem physiologisch verträglichen Salz davon, wobei dieses Verfahren die Umsetzung von Dinatriumiminodiessigsäure mit ω-Chlor-3,5-bis(trifluormethyl)acetanilid und gegebenenfalls die Umsetzung des dadurch erhaltenen Produktes mit einer physiologisch verträglichen Base umfaßt.

14. Verwendung eines Chelates nach Anspruch 1 zur Herstellung eines diagnostischen Mittels für die Verwendung bei der Diagnose des menschlichen oder tierischen Körpers mit Hilfe von NMR-Imaging.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Agent de contraste pour la RMN, comprenant au moins un chélate de métal, paramagnétique, non radioactif, soluble dans l'eau, en même temps qu'au moins un excipient ou véhicule physiologiquement acceptable ou compatible, caractérisé en ce que le chélate en question est un chélate formé avec un agent chélateur de la formule I



(I)

(dans laquelle R^1 à R^5, qui peuvent être identiques ou différents, représentent chacun des atomes d'hydrogène ou d'halogènes, des radicaux carboxyle ou des radicaux alcoxy ou alkyle éventuellement halogénés), ou un sel physiologiquement acceptable de celui-ci.

2. Agent de contraste suivant la revendication 1, caractérisé en ce qu'il comprend de 0,1 à 200 mM du métal paramagnétique précité en solution aqueuse.

3. Agent de contraste suivant l'une quelconque des revendications 1 et 2, caractérisé en ce que le chélate précité est un chélate d'un ion de métal trivalent.

4. Agent de contraste suivant la revendication 3, caractérisé en ce que le chélate précité est un chélate de Fe^{3+}.

5. Agent de contraste suivant la revendication 3, caractérisé en ce que le chélate précité est un chélate de Gd^{3+}.

6. Agent de contraste suivant la revendication 3, caractérisé en ce que le chélate précité est un chélate de Cr^{3+}.

7. Agent de contraste suivant la revendication 6, caractérisé en ce que le chélate précité est un chélate avec l'agent chélateur qu'est l'acide N-(2,6-diéthylphényl-carbamoyl-méthyl)iminodiacétique, ou un sel physiologiquement acceptable de celui-ci.

8. Agent de contraste suivant la revendication 6, caractérisé en ce que le chélate précité est (a) le chélate de chrome (III) de l'acide N-(2,6-diéthylphényl-carbamoyl-méthyl)iminodiacétique; (b) le chélate de chrome (III) du sel de méglumine de l'acide N-(2,6-diéthylphényl-carbamoyl-méthyl)iminodiacétique; (c) le chélate de chrome (III) de l'acide N-(2,6-diméthylphényl-carbamoyl-méthyl)iminodiacétique; ou (d) le chélate de chrome (III) de l'acide N-(2,4,6-triméthylphényl-carbamoyl-méthyl)-iminodiacétique.

9. Agent de contraste suivant la revendication 1, caractérisé en ce que le chélate précité est un chélate avec l'agent chélateur de la formule I (telle que définie dans la revendication 1 et dans laquelle R^1 à R^5 représentent des atomes de fluor, ou bien R^1, R^3 et R^5 représentent des atomes d'hydrogène et R^2 et R^4 représentent des radicaux trifluorométhyle, ou bien R^1 et R^5 représentent des radicaux alkyle en C_1—C_4 et R^2 à R^4 représentent des atomes d'hydrogène), ou un sel physiologiquement acceptable de celui-ci.

10. Chélate paramagnétique, non radioactif, soluble dans l'eau, caractérisé en ce que le groupement chélateur de ce chélate est un composé de la formule I telle que définie dans la revendication 1, ou un sel physiologiquement acceptable de celui-ci.

11. Chélate suivant la revendication 10, caractérisé en ce que c'est un chélate d'un ion de métal paramagnétique, trivalent.

12. Chélate suivant la revendication 11, caractérisé en ce que l'ion de métal précité est Fe^{3+}.

13. Chélate suivant la revendication 11, caractérisé en ce que l'ion de métal précité est Gd^{3+}.

14. Chélate suivant la revendication 11, caractérisé en ce que l'ion de métal précité est Cr^{3+}.

15. Chélate suivant la revendication 14, caractérisé en ce que le groupement chélateur est l'acide N-(2,6-diéthylphényl-carbamoyl-méthyl) iminodiacétique ou un sel physiologiquement acceptable de celui-ci.

16. Chélate suivant la revendication 10, caractérisé en ce que c'est (a) le chélate de chrome (III) de l'acide N-(2,6-diéthylphényl-carbamoyl-méthyl) iminodiacétique; (b) le chélate de chrome (III) du sel de méglumine de l'acide N-(2,6-diéthylphényl-carbamoyl-méthyl)iminodiacétique; (c) le chélate de chrome (III) de l'acide N-(2,6-diméthylphényl-carbamoyl-méthyl)iminodiacétique; ou (d) le chélate de chrome (III) de l'acide N-(2,4,6-triméthylphényl-carbamoyl-méthyl) iminodiacétique.

17. Chélate suivant la revendication 10, caractérisé en ce que dans le composé chélateur précite de la formule I, R^1 à R^5 représentent des atomes de fluor, ou bien R^1, R^3 et R^5 représentent des atomes d'hydrogène et R^2 et R^4 représentent des groupes trifluorométhyle, ou bien R^1 et R^5 représentent des radicaux alkyle en C_1—C_4 et R^2 et R^4 représentent des atomes d'hydrogène.

18. Acide N-[3,5-bis(trifluorométhyl)phénylcarbamoyl-méthyl]iminodiacétique et ses sels physiologiquement acceptables.

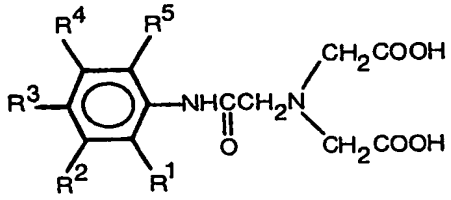
19. Utilisation d'un chélate tel que défini dans la revendication 1 pour la fabrication d'un agent diagnostique à utiliser pour le diagnostic du corps humain ou animal, utilisant l'imagerie à RMN.

20. Procédé de préparation d'un agent de contraste pour RMN, caractérisé en ce que l'on mélange, en solution aqueuse, un agent chélateur de la formule I (telle que définie dans la revendication 1) ou un sel physiologiquement acceptable de celui-ci et au moins un composé de métal paramagnétique, non radioactif, au moins médiocrement soluble dans l'eau.

21. Procédé de préparation d'un chélate paramagnétique, non radioactif, soluble dans l'eau, caractérisé en ce que l'on mélange, en solution aqueuse, un agent chélateur de la formule I (telle que défini dans la revendication 1) ou un sel physiologiquement acceptable de celui-ci et un composé de métal, paramagnétique, non radioactif, au moins médiocrement soluble dans l'eau.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un agent de contraste pour RMN, caractérisé en ce que l'on mélange, en solution aqueuse, un composé de métal, paramagnétique, non radioactif, au moins médiocrement soluble dans l'eau et un agent chélateur, caractérisé en ce que l'agent chélateur en question est un composé de la formule I



(I)

(dans laquelle R^1 à R^5, qui peuvent être identiques ou différents, représentent chacun des atomes d'hydrogène ou d'halogènes, des radicaux carboxyle ou des radicaux alcoxy ou alkyle éventuellement halogénés), ou un sel physiologiquement acceptable de celui-ci.

2. Procédé de préparation d'un agent de contraste pour RMN, lequel procédé comprend le mélange à au moins un excipient ou véhicule physiologiquement acceptable, d'au moins un chélate paramagnétique, non radioactif, soluble dans l'eau, caractérisé en ce qu'à titre de chélate précité, ou utilise un chélate obtenu avec un agent chélateur de la formule I (telle que définie dans la revendication 1) ou avec un sel physiologiquement acceptable de celui-ci.

3. Procédé suivant l'une des revendications 1 et 2, caractérisé en ce que l'on réalise le mélange de manière à obtenir un agent de contraste comprenant de 0,1 à 200 mM du métal paramagnétique précité en solution aqueuse.

4. Procédé suivant l'une quelconque des revendications 1 à 3, caractérisé en ce que l'espèce de métal paramagnétique dans le chélate de métal paramagnétique précité est un ion de métal trivalent.

5. Procédé suivant la revendication 4, caractérisé en ce que le chélate précité est un chélate de Fe^{3+}.

6. Procédé suivant la revendication 4, caractérisé en ce que le chélate précité est un chélate de Gd^{3+}.

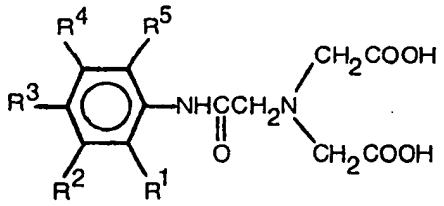
7. Procédé suivant la revendication 4, caractérisé en ce que le chélate précité est un chélate de Cr^{3+}.

8. Procédé suivant la revendication 7, caractérisé en ce que le chélate précité est un chélate avec l'agent chélateur qu'est l'acide N-(2,6-diéthylphényl-carbamoyl-méthyl)iminodiacetique, ou un sel physiologiquement acceptable de celui-ci.

9. Procédé suivant la revendication 7, caractérisé en ce que le chélate précité est (a) le chélate de chrome (III) de l'acide N-(2,6-diéthylphényl-carbamoyl-méthyl)iminodiacétique; (b) le chélate de chrome (III) du sel de méglumine de l'acide N-(2,6-diéthylphényl-carbamoyl-méthyl)iminodiacétique; (c) le chélate de chrome (III) de l'acide N-(2,6-diméthylphényl-carbamoyl-méthyl)iminodiacétique; ou (d) le chélate de chrome (III) de l'acide N-(2,4,6-triméthylphényl-carbamoyl-méthyl) iminodiacétique.

10. Procédé suivant l'une quelconque des revendications 1 et 2, caractérisé en ce que l'agent chélateur précité est un composé de la formule I dans laquelle R^1 à R^5 représentent des atomes de fluor, ou bien R^1, R^3 et R^5 représentent des atomes d'hydrogène et R^2 et R^4 représentent des radicaux trifluorométhyle, ou bien R^1 et R^5 représentent des radicaux alkyle en C_1—C_4 et R^2 à R^4 représentent des atomes d'hydrogène ou un sel physiologiquement acceptable d'un tel composé.

11. Agent de contraste pour RMN, comprenant au moins un chélate de métal, paramagnétique, non radioactif, soluble dans l'eau, en même temps qu'au moins un excipient ou véhicule physiologiquement acceptable, caractérisé en ce que le chélate précité est un chélate avec un agent chélateur de la formule I



(I)

(dans laquelle R^1 à R^5, qui peuvent être identiques ou différents, représentent chacun des atomes d'hydrogène ou d'halogènes, des radicaux carboxyle ou des radicaux alcoxy ou alkyle éventuellement halogénés), ou un sel physiologiquement acceptable de celui-ci.

12. Procédé de préparation d'un chélate paramagnétique, non radioactif, soluble dans l'eau, lequel procédé comprend le mélange, en solution aqueuse, d'un composé de métal, paramagnétique, non radioactif, au moins médiocrement soluble dans l'eau et d'un agent chélateur de la formule I (telle que définie dans la revendication 1) ou un sel physiologiquement acceptable de celui-ci.

13. Procédé de préparation de l'acide N-[3,5-bis(trifluorométhyl)phényl-carbamoyl-méthyl] iminodiacétique ou d'un sel physiologiquement acceptable de celui-ci, ledit procéde comprenant la réaction de l'acide iminodiacétique disodique sur le ω-chloro-3,5-bis(trifluorométhyl)acétanilide et l'éventuelle réaction du produit ainsi obtenu sur une base physiologiquement acceptable.

14. Utilisation d'un chélate tel que défini dans la revendication 1, en vue de la fabrication d'un agent diagnostique à utiliser pour le diagnostic du corps humain ou animal, en utilisant l'imagerie à RMN.